

interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like selectins and integrins. Transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, particularly those having sequence identity with HNK-1 sulfotransferase. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, 93:7108-7113 (1996); U.S. Patent No. 5,536,637]. The results of such efforts are provided herein.

77. PRO474

Enzymatic proteins play important roles in the chemical reactions involved in the digestion of foods, the biosynthesis of macromolecules, the controlled release and utilization of chemical energy, and other processes necessary to sustain life. Glucose dehydrogenase functions in the oxidation of glucose to gluconate to generate metabolically useful energy. The regulation of the PQQ-linked glucose dehydrogenase in different organisms is reviewed in Neijssel, et al., *Antonie Van Leeuwenhoek*, 56(1):51-61 (1989). Glucose dehydrogenase functions as an auxiliary energy generating mechanism, because it is maximally synthesized under conditions of energy stress. In addition to molecules related to glucose dehydrogenase, all novel proteins are of interest. Extracellular and membrane-bound proteins play important roles in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment, usually at a membrane-bound receptor protein.

Secreted proteins have various industrial applications, including use as pharmaceuticals, diagnostics, biosensors and bioreactors. In fact, most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane-bound proteins, also have potential as therapeutic or diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. Membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like selectins and integrins. Transduction of signals that regulate

cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Efforts are being undertaken by both industry and academia to identify new, native secreted and membrane-bound receptor proteins, and particularly cellular proteins and those related to dehydrogenase or oxidoreductase. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted and membrane-bound receptor proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, **93**:7108-7113 (1996); U.S. Patent No. 5,536,637]. The results of such efforts are presented herein.

78. PRO1031

It has been reported that the cytokine interleukin 17 (IL-17) stimulates epithelial, endothelial, and fibroblastic cells to secrete cytokines such as IL-6, IL-8, and granulocyte-colony-stimulating factor, as well as prostaglandin E2. Moreover, it has been shown that when cultured in the presence of IL-17, fibroblasts could sustain proliferation of CD34+ preferential maturation into neutrophils. Thus it has been suggested that IL-17 constitutes an early initiator of the T cell-dependent inflammatory reaction and/or an element of the cytokine network that bridges the immune system to hematopoiesis. See, Yao, et al., *J. Immunol.*, **155**(12):5483-5486 (1995); Fossiez, et al., *J. Exp. Med.*, **183**(6):2593-2603 (1996); Kennedy, et al., *J. Interferon Cytokine Res.*, **16**(8):611-617 (1996). Thus, proteins related to IL-17 are of interest.

More generally, all novel proteins are of interest. Extracellular proteins play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. These secreted polypeptides or signaling molecules normally pass through the cellular secretory pathway to reach their site of action in the extracellular environment.

Secreted proteins have various industrial applications, including pharmaceuticals, diagnostics, biosensors and bioreactors. Most protein drugs available at present, such as thrombolytic agents, interferons, interleukins, erythropoietins, colony stimulating factors, and various other cytokines, are secretory proteins. Their receptors, which are membrane proteins, also have potential as therapeutic or diagnostic agents.

Efforts are being undertaken by both industry and academia to identify new, native secreted proteins, particularly those related to IL-17. Many efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel secreted proteins. Examples of screening methods and techniques are described in the literature [see, for example, Klein et al., *Proc. Natl. Acad. Sci.*, **93**:7108-7113 (1996); U.S. Patent No. 5,536,637]. The results of such efforts are presented herein.

79. PRO938

Protein disulfide isomerase is an enzymatic protein which is involved in the promotion of correct

refolding of proteins through the establishment of correct disulfide bond formation. Protein disulfide isomerase was initially identified based upon its ability to catalyze the renaturation of reduced denatured RNase (Goldberger et al., J. Biol. Chem. **239**:1406-1410 (1964) and Epstein et al., Cold Spring Harbor Symp. Quant. Biol. **28**:439-449 (1963)). Protein disulfide isomerase has been shown to be a resident enzyme of the endoplasmic reticulum which is retained in the endoplasmic reticulum via a -KDEL or -HDEL amino acid sequence at its C-terminus. Protein disulfide isomerase and related proteins are further described in Laboisserie, et al., J. Biol. Chem., **270**(47):28006-28009 (1995); Jeenes, et al., Gene, **193**(2):151-156 (1997); Koivunen, et al., Genomics, **42**(3):397-404 (1997); Desilva, et al., DNA Cell Biol., **15**(1):9-16 (1996); Freedman, et al. Trends in Biochem. Sci. **19**:331-336 (1994); Bulleid, N.J. Advances in Prot. Chem. **44**:125-50 (1993); and Noiva, R., Prot. Exp. and Purification **5**:1-13 (1994). These studies indicate the importance of the identification of protein disulfide related proteins.

More generally, and also of interest are all novel membrane-bound proteins and receptors. Such proteins can play an important role in the formation, differentiation and maintenance of multicellular organisms. The fate of many individual cells, e.g., proliferation, migration, differentiation, or interaction with other cells, is typically governed by information received from other cells and/or the immediate environment. This information is often transmitted by secreted polypeptides (for instance, mitogenic factors, survival factors, cytotoxic factors, differentiation factors, neuropeptides, and hormones) which are, in turn, received and interpreted by diverse cell receptors or membrane-bound proteins. Such membrane-bound proteins and cell receptors include, but are not limited to, cytokine receptors, receptor kinases, receptor phosphatases, receptors involved in cell-cell interactions, and cellular adhesion molecules like selectins and integrins. For instance, transduction of signals that regulate cell growth and differentiation is regulated in part by phosphorylation of various cellular proteins. Protein tyrosine kinases, enzymes that catalyze that process, can also act as growth factor receptors. Examples include fibroblast growth factor receptor and nerve growth factor receptor.

Membrane-bound proteins and receptor molecules have various industrial applications, including as pharmaceutical and diagnostic agents. Receptor immunoadhesins, for instance, can be employed as therapeutic agents to block receptor-ligand interaction. The membrane-bound proteins can also be employed for screening of potential peptide or small molecule inhibitors of the relevant receptor/ligand interaction.

Given the importance of membrane bound proteins, efforts are under way to identify novel membrane bound proteins. Moreover, given the importance of disulfide bond-forming enzymes and their potential uses in a number of different applications, for example in increasing the yield of correct refolding of recombinantly produced proteins, efforts are currently being undertaken by both industry and academia to identify new, native proteins having sequence identity with protein disulfide isomerase. Many of these efforts are focused on the screening of mammalian recombinant DNA libraries to identify the coding sequences for novel protein disulfide isomerase homologs.

We herein describe the identification and characterization of a novel polypeptide having homology to protein disulfide isomerase.

PRO1082

The low density lipoprotein (LDL) receptor is a membrane-bound protein that plays a key role in